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(71) Applicant(s)

**Glaxo Group Limited**  
(Incorporated in the United Kingdom)  
**Glaxo House, Berkeley Avenue, GREENFORD,**  
**Middlesex, UB6 0NN, United Kingdom**

(72) Inventor(s)

**Frank Peter Grassler**

(74) Agent and/or Address for Service

**Michael A Reed**  
**Glaxo Wellcome PLC, Glaxo Wellcome House,**  
**Berkeley Avenue, GREENFORD, Middlesex, UB6 0NN,**  
**United Kingdom**

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**B58Y B586**  
**U1S S2414**

(56) Documents Cited

**EP 0171227 A**

(58) Field of Search

**UK CL (Edition Q ) A5B BHA BJA**  
**INT CL<sup>6</sup> A61K 31/135**  
**ONLINE: CAS ONLINE, EPODOC, JAPIO, WPI**

(54) Abstract Title

**Compositions comprising bupropion for the treatment of premature ejaculation**

(57) A composition comprising bupropion, or physiologically acceptable salts, solvates or enantiomers thereof, is used for the treatment of premature ejaculation that is either caused by a physical disorder or that is induced by a cGMP phosphodiesterase (PDE) inhibitor or a cGMP PDE V inhibitor, such as sildenafil. The composition may comprise bupropion and sildenafil for the treatment of erectile dysfunction and sildenafil induced premature ejaculation.

**GB 2 340 037 A**

### Medicament for Treating Premature Ejaculation

This application claims priority to US Provisional Application 60/094,701 filed July 30, 1998, the entire disclosure of which is considered part of this application and is herein incorporated by reference.

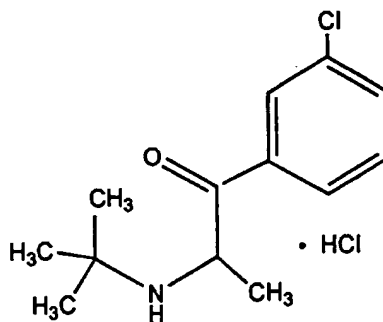
This invention relates to a new medical use for and compositions containing  
5 bupropion and physiologically acceptable salts and solvates thereof. The invention concerns use of bupropion in treating premature ejaculation that is primarily caused by a physical disorder. Specifically the invention concerns the use of bupropion in treating premature ejaculation, which is sometimes induced following administration of sildenafil or other cGMP PDE and PDE V inhibitors.  
10 The invention also concerns pharmaceutical compositions comprising bupropion and sildenafil.

Bupropion hydrochloride,  $(\pm)$ -1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride, is the active ingredient of Wellbutrin® and Wellbutrin®SR which are marketed in the United States for the treatment of  
15 depression. It is also the active ingredient of Zyban® which is marketed in the United States as an aid to smoking cessation. The term "bupropion" herein includes all physiologically acceptable salts and solvates thereof and all enantiomers thereof.

Sildenafil citrate, 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo [4,3-  
20 d]pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate, is the active ingredient in VIAGRA®, which is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) and is marketed in the United states as an oral therapy for erectile dysfunction. The term "sildenafil" herein includes all physiologically acceptable salts and solvates  
25 thereof.

Bupropion is a relatively weak inhibitor of the neuronal uptake of noradrenaline (NA), serotonin and dopamine (DA), and does not inhibit monoamine oxidase. While the mechanism of action of bupropion, as with other antidepressants, is unknown, it is presumed that this action is mediated by noradrenergic and/or

dopaminergic mechanisms. Available evidence suggests that bupropion is a selective inhibitor of noradrenaline (NA) at doses that are predictive of antidepressant activity in animal models. See Ascher, J.A., et al., Bupropion: A Review of its Mechanism of Antidepressant Activity. *Journal of Clinical*  
 5 *Psychiatry*, 56: p. 395-401,1995.

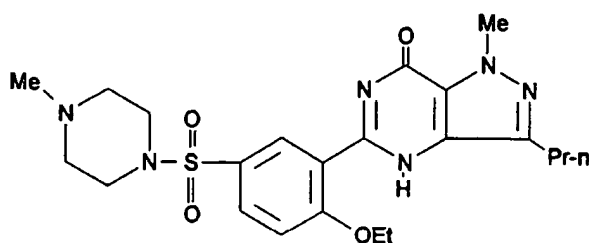


Bupropion HCl

It has also been disclosed that bupropion is useful for the treatment of migraine (U.S. 5,753,712), reducing cholesterol (U.S. 4,438,138), treatment of minimal  
 10 brain dysfunction (U.S. 4,435,449), treatment of tardive dyskinesia (U.S. 4,425,363), reversing impaired mental alertness due to ethanol consumption (U.S. 4,393,078) and suppressing prolactin secretion (U.S. 4,347,257).

It has further been disclosed in U.S. 4,507,323 that bupropion is useful for the treatment of psychosexual dysfunction, e.g., premature ejaculation, wherein said  
 15 dysfunctions are those in which a physical disorder or another AXIS I mental disorder, e.g., major depression, is not the primary cause of disturbance in sexual function.

Sildenafil is disclosed, for example in European Patent No 463756 and may be represented by the formula



(III)

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The compounds described in the aforementioned patent specification are described as potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs). EP-A-0463756 and EP-A-0526004 describe such cGMP PDE inhibitors as having utility in the treatment of stable, unstable, and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency, e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS). WO94/28902 discloses the use of cGMP PDE inhibitors in treating male erectile dysfunction. Sildenafil is normally administered as an oral dosage form, typically a tablet, containing 25mg, 50mg or 100mg of the active ingredient.

Later publications, for example Eardley, I. *Exp. Opin. Invest. Drugs* (1997) 6 (12) 1803-1810 have confirmed that sildenafil is a specific inhibitor of the particular physiological isoform (Type V) of the cGMP PDE enzyme found in the penis. Thus, sildenafil can also be described as a PDE V inhibitor.

It has been found that premature ejaculation is sometimes induced following administration of the drug sildenafil. Other cGMP PDE, particularly PDE V inhibitors may also induce premature ejaculation.

5 Surprisingly, it has been found that bupropion is useful for the treatment of premature ejaculation that is primarily caused by a physical disorder. Specifically, it has been found that bupropion is useful for the treatment of cGMP PDE and PDE V inhibitor-induced premature ejaculation and not merely premature ejaculation related to psychosexual dysfunction (U.S. 4,507,323).  
10 More specifically, it has been found that bupropion is useful for the treatment of sildenafil-induced premature ejaculation.

According to one aspect of the present invention, there is provided a method of treating a human suffering from or susceptible to premature ejaculation that is primarily caused by a physical disorder comprising administering an effective amount of bupropion.

15 According to a second aspect of the present invention, there is provided a method of treating a human suffering from or susceptible to premature ejaculation induced by cGMP PDE inhibitors which comprises administering an effective amount of bupropion.

20 According to a third aspect of the invention, there is provided a method of treating a human suffering from or susceptible to premature ejaculation induced by cGMP PDE V inhibitors which comprises administering an effective amount of bupropion.

25 According to a fourth aspect of the invention, there is provided a method of treating a human suffering from or susceptible to premature ejaculation induced by sildenafil which comprises administering an effective amount of bupropion.

The invention also provides, in a fifth aspect, pharmaceutical compositions for the treatment of premature ejaculation primarily caused by a physical disorder or

premature ejaculation induced by cGMP PDE inhibitors, cGMP PDE V inhibitors or sildenafil comprising bupropion as the active ingredient.

According to a sixth aspect of the present invention there is provided the use of bupropion in the manufacture of a medicament for the treatment of a human  
5 suffering from or susceptible to premature ejaculation primarily caused by a physical disorder or premature ejaculation induced by cGMP PDE, cGMP PDE V inhibitors or sildenafil.

The invention further provides, in a seventh aspect, pharmaceutical compositions comprising bupropion and sildenafil (useful for the treatment of erectile  
10 dysfunction and sildenafil-induced premature ejaculation).

Compounds for use in the invention are suitably in the form of physiologically acceptable salts. These salts may include acid addition salts formed with organic or inorganic acids for example hydrochlorides, hydrobromides, sulphates, nitrates, phosphates, formates, mesylates, citrates, benzoates fumarates,  
15 maleates and succinates. Wellbutrin®, Wellbutrin®SR and Zyban® employ the hydrochloride salt of bupropion. VIAGRA® employs the citrate salt of sildenafil.

Bupropion and/or sildenafil for use according to the invention may be administered as the raw chemical comprising the active compound. However, one or more of the following pharmaceutically acceptable formulations may also  
20 be employed. Conveniently, a compound for use according to the invention may be formulated in conventional manner using one or more pharmaceutically acceptable excipients. Thus, a compound for use according to the invention may for example be formulated for oral, sub-lingual, buccal, parenteral, rectal or intranasal administration or in a form suitable for administration by inhalation or  
25 insufflation (either through the mouth or nose).

For oral administration the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g.

pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art.

Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (following HBr removal sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl P-hydroxybenzoates or sorbic acid).

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

A compound for use according to the invention may be formulated for parenteral administration by injection, conveniently intravenous, in intramuscular or subcutaneous injection. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, optionally with an added preservative.

The compositions for parenteral administration may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in dry form such as a powder, crystalline or freeze-dried solid for constitution with a suitable vehicle, e.g. sterile pyrogen-free water or isotonic saline before use. They may be presented, for example, in sterile ampoules or vials.

A compound for use according to the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glyceride.

5     Tablets for sub-lingual administration may be formulated in a conventional manner.

For intranasal administration a compound for use according to the invention may be used, for example, as a liquid in the form of a spray or drops or as a powder. Suitably the preparation for intranasal administration is delivered in the form of a spray or aerosol from an insufflator or from a pressurised pack or nebuliser with  
10     the use of a suitable propellant.

For administration by inhalation the compound for use according to the invention is conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane,  
15     carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of use in the invention and a suitable powder base such as lactose or starch.

20     Various formulations of bupropion have been disclosed in U.S. 5,427,798, U.S. 5,358,970, U.S. 5,541,231 and U.S. 5,731,000 (and other patents related to U.S. 5,358,970).

It will be appreciated that the precise dose administered will depend on the particular compound used, the age and condition of the patient and the  
25     frequency and route of administration and will be at the ultimate discretion of the attendant physician. The compound may be administered in single or divided doses and may be administered one or more times, for example 1 to 4 times per day.



Typically, bupropion is useful for the treatment of cGMP PDE inhibitor-, cGMP PDE V inhibitor- or sildenafil-induced premature ejaculation in an amount between 0.1 mg to 500 mg per day, more preferably in an amount between 25 mg and 300 mg per day and most preferably in an amount between 150 mg to 5 300 mg per day.

Typically, pharmaceutical compositions comprising bupropion and sildenafil (useful for the treatment of erectile dysfunction and sildenafil-induced premature ejaculation) comprise bupropion in the amount of 0.1 mg to 300 mg per unit dose, more preferably in an amount between 25 mg and 300 mg per unit dose 10 and most preferably in an amount between 50 mg to 150 mg per unit dose and further comprise sildenafil in the in an amount between 1 mg to 200 mg per unit dose, preferably in an amount between 25 mg to 200 mg per unit dose and more preferably in an amount between 25 mg to 100 mg per unit dose.

What is claimed is:

1. A method of treating a human suffering from or susceptible to premature ejaculation that is primarily caused by a physical disorder comprising  
5 administering an effective amount of bupropion.
2. A method of treating a human suffering from or susceptible to premature ejaculation induced by cGMP PDE inhibitors which comprises administering an effective amount of bupropion.
3. A method of treating a human suffering from or susceptible to premature  
10 ejaculation induced by cGMP PDE V inhibitors which comprises administering an effective amount of bupropion.
4. A method of treating a human suffering from or susceptible to premature ejaculation induced by sildenafil which comprises administering an effective amount of bupropion.
- 15 5. A pharmaceutical composition for treating a human suffering from or susceptible to premature ejaculation that is primarily caused by a physical disorder which comprises bupropion as the active ingredient.
6. A pharmaceutical composition for treating a human suffering from or susceptible to premature ejaculation induced by cGMP PDE inhibitors which  
20 comprises bupropion as the active ingredient.
7. A pharmaceutical composition for treating a human suffering from or susceptible to premature ejaculation induced by cGMP PDE V inhibitors which comprises bupropion as the active ingredient.
8. A pharmaceutical composition for treating a human suffering from or  
25 susceptible to premature ejaculation induced by sildenafil which comprises bupropion as the active ingredient.



Application No: GB 9917346.0  
Claims searched: 1-8

Examiner: Dr Paul D Jenkins  
Date of search: 29 September 1999

**Patents Act 1977**  
**Search Report under Section 17**

**Databases searched:**

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK CI (Ed.Q): A5B (BHA, BJA)

Int CI (Ed.6): A61K 31/135

Other: Online: CAS Online, EPODOC, JAPIO, WPI

**Documents considered to be relevant:**

Category	Identity of document and relevant passage	Relevant to claims
X	EP 0171227 A1 (WELLCOME) see page 1, line 1 to page 2, line 24	1-8

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.